#33 | Appeal E
Gadm

PATENT
ATTORNEY DOCKET 27866/32663

OIPE JC35 JUL 10 1998 PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application of:	)	For: Methods for Using Agents that Bind to VCAM-1
Masinovsky *et al.*	)	
	)	Group Art Unit: 1806
Serial No: 08/448,649	)	
	)	
Filed: May 24, 1995	)	Examiner: P. Gambel, Ph.D.

APPELLANTS' BRIEF UNDER 37 C.F.R. §1.192

RECEIVED
JUL 22 1998
GROUP 180(

Li-Hsien Rin-Laures, M.D.
Registration No. 33,547
MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN
6300 Sears Tower
233 S. Wacker Drive
Chicago, IL 60606-6402
(312) 474-6300

07/16/1998 MMARMOL 00000061 08448649
02 FC:220 155.00 OP

July 8, 1998

RECEIVED
JUL 21 1998
GROUP 1800

TABLE OF CONTENTS

APPELLANTS BRIEF

1. REAL PARTY IN INTEREST

Fred Hutchinson Cancer Research Center, Seattle, Washington is the real party in interest by virtue of an assignment from the inventors recorded on September 20, 1990 at Reel 5464, Frame 0501 in the U.S. Patent and Trademark Office with respect to grandparent application U.S. Serial No. 07/562,008 filed August 1, 1990. ICOS Corporation, Bothell, Washington is the exclusive licensee of the subject matter of the application.

2. RELATED APPEALS AND INTERFERENCES

There are presently no pending appeals or interferences related to the present application.

3. STATUS OF CLAIMS

Claims 30-33 are currently pending in the application in the form set out in Exhibit A attached hereto and stand rejected under 35 U.S.C. §112, first paragraph, for assertedly lacking written descriptive support and enablement for reasons set out in the Office Action mailed October 3, 1997 attached hereto as Exhibit B and the prior Office Action mailed March 20, 1997 attached hereto as Exhibit C.

The present application is a file wrapper continuation of U.S. patent application Serial No. 08/051,455 (abandoned) which in turn was a division of U.S. patent application Serial No. 07/562,008 (U.S. Patent No. 5,206,345).

4. STATUS OF AMENDMENTS

No "after final" amendments were requested. The last amendment to be entered was in conjunction with Appellants' submission under 37 C.F.R. §1.129(a) mailed September 19, 1997.

5. SUMMARY OF THE INVENTION

The general field of the invention is the use of antibodies to block interaction between cell surface adhesion molecules. All pending claims 30-33 are directed to a method of using an antibody that binds to vascular cell adhesion molecule-1 (VCAM-1) to block adhesion between: (1) a bone marrow stromal cell expressing VCAM-1 and (2) a cell expressing the molecule VLA-4 (very late antigen-4). Within the bone marrow, the stromal cells form part of the supporting layer or matrix of cells underlying the hemopoietic cells (*i.e.*, the cells which generate new blood cells, including red blood cells, lymphocytes, monocytes, etc.). See page 16, lines 25-37 of the specification. Blocking adhesion of hemopoietic cells to stromal cells results in release of hemopoietic cells into peripheral blood circulation and provides important therapeutic effects in, for example, the field of bone marrow transplantation. In bone marrow donors, release of hemopoietic precursor cells allows these cells to be easily harvested from the peripheral blood, while in bone marrow recipients, release of hemopoietic cells could be used as part of a regime to eliminate the recipient's own bone marrow prior to transplantation.

Prior to the August 1, 1990 effective filing date of the present application, VCAM-1 had been identified on endothelial cells (cells lining the interior surface of blood vessels), and its gene had been cloned and partially characterized. The β_1 integrin VLA-4 was known to be present on lymphocytes and had been shown to bind not only VCAM-1 but also fibronectin (a component of the extracellular matrix). The interaction between VCAM-1 and VLA-4 was believed to be involved in mediating lymphocyte adhesion to endothelial cells. See page 2, lines 33-36 and page 8, line 34 through page 9, line 12 of the specification.

The present claims are based on Appellants' discovery that VCAM-1 is expressed on bone marrow stromal cells, a cell type not previously known to express this molecule. See page 17, lines 3-14 of the specification. Independent claim 30 is thus directed to methods of blocking VCAM-1-mediated interaction between bone marrow stromal cells expressing VCAM-1 and cells expressing VLA-4. This category of "cells expressing VLA-4" encompasses any of the cell types that express VLA-4, including lymphocytes and hemopoietic cells. The application's disclosure of a representative embodiment of an anti-VCAM-1 antibody that blocks VCAM-1-mediated intercellular interactions, the 6G10 monoclonal antibody produced by hybridoma ATCC

No. HB 10519, is the basis for the recitation in dependent claim 31 of monoclonal antibodies and fragments thereof that bind to the epitope recognized by antibody 6G10. See page 4, lines 11-16 of the specification.

The claims are further based on Appellants' related discovery that VLA-4 is expressed at high levels on hemopoietic cells bearing the CD34 antigen, a subset of hemopoietic cells rich in stem cells and progenitor cells, and Appellants' conclusion from this discovery that interaction between VCAM-1 and VLA-4 mediates adhesion between bone marrow stromal cells and hemopoietic stem and progenitor cells. See page 17, lines 24-33 of the specification. Accordingly, dependent claims 32 and 33 specify that the cell expressing VLA-4 is a hemopoietic precursor cell bearing the CD34 antigen (claim 32) or is a hemopoietic stem or progenitor cell (claim 33).

6. ISSUES PRESENTED

1. When declaration evidence was presented in response to the rejection of claims 30-33 under 35 U.S.C. §112, first paragraph, for allegedly lacking written descriptive support in the specification, was it error for the Examiner to disregard this evidence and to rely on enablement considerations in maintaining the written description rejection?

2. When declaration evidence was presented in response to the rejection of claims 30-33 under 35 U.S.C. §112, first paragraph, for allegedly lacking enablement, was it error for the Examiner to disregard this evidence and to rely on written description considerations in maintaining the enablement rejection?

7. GROUPING OF CLAIMS

Claims 30-33 are rejected on identical grounds, but do not stand or fall together. The language recited in each claim is different and thus each claim has different bases for written descriptive support and enablement. For example, independent claim 30 recites a "cell expressing VLA-4," a term that characterizes a variety of cell types including lymphocytes and hemopoietic cells, while dependent claims 32 and 33 specifically recite "hemopoietic" cells. Patentability of the claims is argued separately below.

8. PATENTABILITY ARGUMENTS

The Appellants submit that adequate written descriptive support for each of claims 30-33 appears in the specification and that each of the claims is fully enabled by the specification. The outstanding rejections under 35 U.S.C. §112, first paragraph, should therefore be reversed with respect to all claims.

A. The Specification and Relevant Prosecution History

Exemplary portions of the specification that address the claimed invention are reproduced here for convenience. The Background of the Invention at page 2, lines 33-36 notes the role of VCAM-1/VLA-4 interaction in adhesion between endothelial cells (expressing VCAM-1) and lymphocytes (expressing VLA-4):

> Recently, vascular cell adhesion molecule-1 (VCAM-1) was identified as a TNF- and IL1-inducible ligand for VLA4-mediated attachment of lymphocyte adhesion to human umbilical vein endothelial cells (HUVEC) (28-30). [Emphasis added.]

With respect to the role of VCAM-1/VLA-4 interactions in adhesion between bone marrow stromal cells (expressing VCAM-1) and hemopoietic cells (expressing VLA-4), page 17, lines 3-14 and 24-33 state that:

> We have discovered that the [VCAM-1] antigen recognized by mAb [monoclonal antibody] 6G10 is expressed on human bone marrow stromal cells *in vitro* especially after induction with IL-4 [interleukin-4] and/or TNF [tumor necrosis factor]. . . . .
> This novel finding would not have been predicted a priori from available information about the tissue distribution of VCAM-1.
>
> * * * *
>
> Further, we have discovered that a major receptor for VCAM-1, VLA-4 (also known as integrin alpha4/beta1 (69)), is expressed at high levels on bone marrow cells bearing the CD34 antigen. . . . . This finding of coexpression [of VLA-4 and CD34] is significant because CD34 expression distinguishes a subset of bone marrow cells (1-4%) which are enriched in primitive stem cells and progenitors (70). Therefore, we infer that adhesive interactions within the bone marrow between hemopoietic stem cells and/or progenitor cells and stromal elements may be mediated by the

binding of VLA-4 and the [VCAM-1] antigen recognized by 6G10. [Emphasis added.]

The Summary of the Invention at page 4, lines 11-16 also notes that contemplated binding partners of VCAM-1, of which a representative embodiment is the 6G10 monoclonal antibody, are preferably characterized by the ability to block binding of lymphocytes (which express VLA-4) to endothelial cells (which express VCAM-1) and "most preferably" by the ability to bind human VCAM-1 and bone marrow stromal cells (expressing VCAM-1):

> The binding partners are preferably also characterized by the ability to block lymphocyte binding to cytokine-activated endothelial cells, and most preferably by binding to human VCAM-1 and to IL4- or TNFα-activated bone marrow stromal cells. A representative embodiment of this most preferred binding partner is mAb 6G10 . . . [Emphasis added.]

1. The Written Description Rejection

Prior to the March 20, 1997 Action, claim 30 recited "hemopoietic precursor cell" rather than "cell expressing VLA-4." In rejecting this claim and its dependent claims for lack of written descriptive support in the March 20, 1997 Action (Exhibit C), the Examiner stated that the passage at page 17, lines 24-33 "refers to the expression of VLA-4 on human CD34+ bone marrow cells and infers that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements and go on further to disclose the use of VCAM-1-specific antibodies to prevent GVHD [graft vs. host disease]." The Examiner characterized the passage at page 4, lines 11-16 as "refer[ring] to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors." The Examiner then concluded that:

> There does not appear to be support for interfering with hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion such as useful in inhibiting GVHD [graft vs. host disease] and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion. [Emphasis in original.]

In response, Appellants submitted a Second Declaration of Beverly Torok-Storb, Ph.D., Under 37 C.F.R. §1.132 (attached hereto as Exhibit D) to support their position, and also subsequently amended claim 30 to recite "cell expressing VLA-4." The Examiner nevertheless maintained the written description rejection of claim 30 in the October 3, 1997 Action (Exhibit B) because the claim as amended encompassed cells other than lymphocytes. In doing so, the Examiner also improperly introduced enablement considerations, stating that "In contrast to applicant's reliance on the instant disclosure including Example 5 and the expression of VLA-4 on hemopoietic cells; the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD . . . . [Emphasis added.]" (Page 3, fourth paragraph of Action.)

After stating in the October 3, 1997 Action (Exhibit B) that "Applicant's amendment in conjunction with the Torok-Storb and Papayannoupoulo declarations . . . have been fully considered but are not found convincing," the Examiner proceeded to restate not only aspects of Dr. Torok-Storb's Exhibit D declaration but also aspects of the Second Declaration of Thalia Papayannopoulou, M.D., Dr. Sci., Under 37 C.F.R. §1.132 (attached hereto as Exhibit F and discussed below in section C.), which was presented on the issue of enablement rather than written description. (See page 3, last paragraph and page 4, first two paragraphs of the Action.) Without identifying any potential insufficiency of the declaratory evidence or providing any rebuttal evidence to the factual representations of the declaration, the Examiner summarily maintained the written description rejection and also addressed enablement considerations (guidance and direction on "how to use") in the next paragraph:

> The examiner maintains that the application as filed does not provide written description nor guidance and direction on "how to use" anti-VCAM-1 to block any VCAM-1-mediated adhesion, regardless of the type of cells involved, to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells. [Page 4, third paragraph; emphasis added.]

2. The Enablement Rejection

Prior to the October 3, 1997 Action, Appellants had submitted extensive declaratory evidence supporting enablement of the claimed invention, in the form of a (first) Declaration of Beverly J. Torok-Storb, Ph.D. Under 37 C.F.R. §1.132 (attached hereto as Exhibit E), Dr. Torok-Storb's Exhibit D declaration, and a Second Declaration of Thalia Papayannopoulou, M.D., Dr. Sci, Under 37 C.F.R. §1.132 (attached hereto as Exhibit F).

Dr. Torok-Storb's Exhibit E declaration was submitted in response to the Examiner's statements in a prior Office Action that:

> In addition, it is not clear what is the therapeutic benefit of decreasing adhesion of bone marrow cells to bone marrow stromal cells. The disclosure appears to indicate the use of the instant 6G10 antibody either to ameliorate inflammatory conditions (Summary of the Invention), the claims of which have been canceled; or to promote bone marrow transplantation (Example 5). How do the claimed methods promote bone marrow transplantation or hemopoiesis? [Emphasis added.]

Her declaration responded by explaining the therapeutic benefits for bone marrow transplantation that would arise from blocking hemopoietic progenitor adhesion to stromal cells and consequentially releasing bone marrow cells into the peripheral bloodstream.

Dr. Torok-Storb's Exhibit D declaration and Dr. Papayannopoulou's Exhibit F declaration were submitted in response to the March 20, 1997 Action. After stating in the October 3, 1997 Action (page 5) that ". . . Applicant's arguments and declaratory evidence, filed 8/22/97 (Paper No. 26) have been fully considered but are not found convincing for the reasons of record and reiterated above," the Examiner summarily maintained the enablement rejection without identifying any potential insufficiency of the declaratory evidence or providing any evidence in rebuttal to the factual representations of the declarations. The Examiner also linked the alleged lack of written description of the claimed invention with a lack of disclosure of "how to use" the antibodies according to the claimed invention, stating that:

> The examiner maintains that the application as filed does not provide written description nor guidance and direction on "how to use" anti-VCAM-1 to block any VCAM-1-mediated adhesion,

> regardless of the type of cells involved, to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells.
>
> Therefore, the specification as filed does not provide any guidance on "how to use" the VCAM-1 specific antibodies in the manner encompassed by the claims or argued by applicants in conjunction with Torok-Storb and Papayannoupoulo or any other manner as encompassed by the claimed methods. The specification is drawn to inhibiting lymphocyte adherence not hemopoietic stem and progenitor cell adherence. The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods. [Page 5, sixth and seventh paragraphs; emphasis added.]

B. The Rejection For Lack of Written Descriptive Support Should Be Reversed

1. The Examiner Erred by Essentially Requiring *In Ipsis Verbis* Disclosure

In acknowledging that the specification described the VCAM-1-VLA-4 interaction between hemopoietic cells and stromal cells, yet rejecting Appellants' claims for lacking written description simply because words like "blocking interaction with antibody" did not appear in the same sentence, the Examiner essentially required *in ipsis verbis* support for Appellants' claims. This was error because the disclosure need only "convey with reasonable clarity" to persons skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. *In re Alton*, 37 USPQ2d 1578, 1581 (Fed. Cir. 1996). In *Alton*, the Court of Appeals for the Federal Circuit stated that:

> In order to meet the adequate written description requirement, the applicant does not have to utilize any particular form of disclosure to describe the subject matter claimed, but 'the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed.' *Alton*, 37 USPQ2d at 1581 (quoting *In re Gosteli*, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989)). [Emphasis added.]

It is axiomatic that the essential characteristic of antibodies is their ability to bind to a molecule, and a major therapeutic application of antibodies lies in their ability to block binding of that molecule to other molecules. With regard to the disclosure of the present

specification, Dr. Torok-Storb's Exhibit D declaration states in paragraph 6 that "one of ordinary skill in the art would understand from reading the application that anti-VCAM-1 antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved. [Emphasis added.]" The declaration thus directly contradicts the Examiner's position that Appellants contemplated use of anti-VCAM-1 antibodies to block adhesion of only one type of cell expressing VLA-4 (*i.e.*, lymphocytes) and not hemopoietic cells.

The specification identifies both lymphocytes and hemopoietic cells as VLA-4 expressing cells that are involved in such VCAM-1/VLA-4 mediated adhesion. In addition, the specification identifies both endothelial cells and bone marrow stromal cells as VCAM-1 expressing cells that are involved in such VCAM-1/VLA-4 mediated adhesion. This is confirmed by paragraphs 4 and 5 of Dr. Torok-Storb's Exhibit D declaration, which explain that the specification discloses that VCAM-1 plays a role in the adhesive interaction between hemopoietic precursor cells (which express VLA-4) and bone marrow stromal cells (which express VCAM-1), as illustrated in Figure 1 below, and that VCAM-1 also mediates adhesive interactions between lymphocytes (which express VLA-4) and activated endothelial cells (which express VCAM-1), as illustrated in Figure 2 below.

FIG. 1

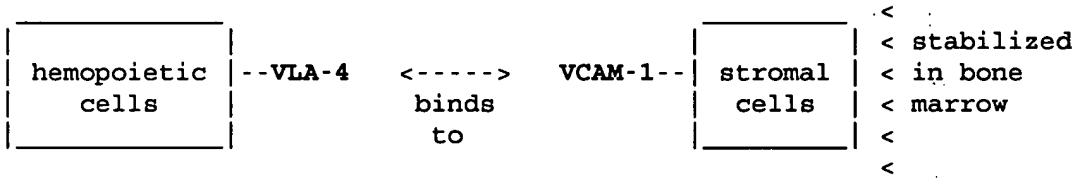
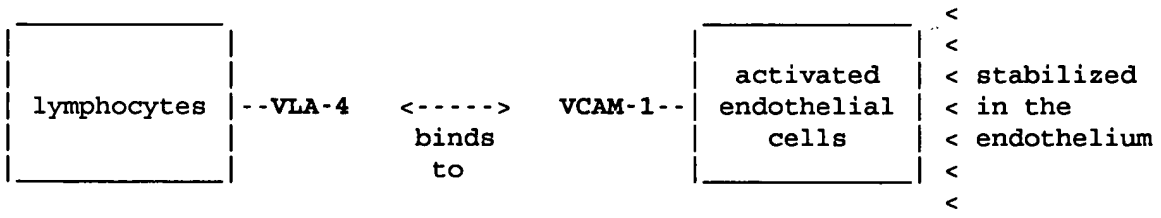


FIG. 2



Paragraph 6 of Dr. Torok-Storb's Exhibit D declaration concludes that: "There is no indication in the application that the use of VCAM-1-specific antibodies to interfere with, or block, intercellular adhesive interactions is limited to only some of the disclosed VCAM-1-

mediated interactions and not others." Thus, Dr. Torok-Storb's declaration demonstrates that the specification "conveys with reasonable clarity" that anti-VCAM-1 antibodies are useful in the broad genus of methods for blocking adhesion between any cell expressing VCAM-1 and any cell expressing VLA-4. Given that the specification highlights the identification of VCAM-1 on bone marrow stromal cells as a "novel finding," one clearly recognizable subgenus of such VCAM-1/VLA-4 adhesive interactions is the interaction between bone marrow stromal cells expressing VCAM-1 and cells expressing VLA-4, as recited in claim 30.

With respect to the specific interaction between bone marrow stromal cells and hemopoietic cells that is the subject of claims 32-33, paragraph 7 of Dr. Torok-Storb's Exhibit D declaration states that: "One of ordinary skill in the art as of August 2, 1990 would have clearly understood upon reading the application, particularly the quoted portion at page 4, lines 11-16, that the Applicants taught use of anti-VCAM-1 antibody to inhibit any VCAM-1-mediated adhesive interaction, including the disclosed adhesive interaction between stromal cells and hemopoietic precursor cells . . . [Emphasis added.]"

Applying the graphic analogy of "blaze marks" in a forest of trees recently re-utilized by the Federal Circuit in *Fujikawa v. Wattanasin*, 39 USPQ2d 1895, 1905 (Fed. Cir. 1996) (citing *In re Ruschig*, 154 USPQ 118 (CCPA 1967), it is clear that Appellants have not only put blaze marks on bone marrow stromal cells as an important subset of cells expressing VCAM-1, but have also emphasized the specific interaction between bone marrow stromal cells and hemopoietic cells. See page 17, lines 3-14 and 24-33 of the specification. Appellants' identification of VLA-4 expression on a subset of bone marrow cells expressing the CD34 antigen and the disclosure that this subset of cells is rich in stem and progenitor cells (page 17, lines 24-33 of the specification) provides a clear basis for the specific recitation in claim 32 of hemopoietic cells expressing CD34 antigen and the recitation in claim 33 of hemopoietic stem cells or progenitor cells.

For these reasons, the Examiner's position, that Appellants contemplated blocking adhesion of only lymphocytes and not hemopoietic cells, is simply not a reasonable interpretation of what the specification's disclosure conveyed to one of ordinary skill in the art as of August 1,

1990. The rejection under 35 U.S.C. §112, first paragraph, for lack of written descriptive support should therefore be reversed with respect to all claims 30-33.

2. The Examiner Erred by Summarily Dismissing Declaratory Evidence Addressing Whether the Specification Adequately Described the Claimed Subject Matter

Appellants submit that the Examiner also erred by summarily dismissing, without adequate explanation, the Exhibit D Declaration of Dr. Beverly Torok-Storb. A similar situation was held to be error on the examiner's part in *Alton*, where the Federal Circuit stated:

> The examiner also erred by dismissing the Wall declaration without an adequate explanation of why the declaration failed to overcome the prima facie case initially established by the Board — the rejection on the ground that the application failed to describe the subject matter of claim 70. *Alton*, 37 USPQ2d at 1583.

Although the Examiner stated in the October 3, 1997 Action (Exhibit B, pages 3-4, section 6) that he had considered the declaratory evidence, there was no explanation of why this declaratory evidence was insufficient to overcome the written description rejection, nor was there any evidence supplied in rebuttal. After the Examiner restated one aspect of Dr. Torok-Storb's Exhibit D declaration ("that one of ordinary skill in the art would understand from reading the application that anti-VCAM antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved and that one of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4-VCAM-1 interaction to another"), he summarily concluded that the rejection should be maintained.[1]

Upon consideration of the totality of the record, including Appellants' uncontroverted declaratory evidence, it is clear that the rejection under 35 U.S.C. §112, first

---

[1] Although a subsequent paragraph contains a confusing characterization of the amended claims as "an amendment to correct an obvious error" and states that "Obviousness is not the standard for addition [of] new limitations," this objection does not apply to Appellants' declaratory evidence. Dr. Torok-Storb's declaration nowhere states that she draws her conclusions from what was "obvious" to one of ordinary skill in the art at the time. She merely explains what "one of ordinary skill in the art would understand from reading the application" (see paragraphs 2 and 6 of Dr. Torok-Storb's Exhibit D declaration).

paragraph, for lack of written descriptive support should be reversed with respect to each of claims 30-33.

3. The Examiner Erred by Introducing Enablement Considerations

The Examiner erred by improperly introducing considering enablement-type issues when rejecting claims 30-33 based on alleged lack of written description in the specification. The written description and enablement requirements are "separate and distinct" requirements of 35 U.S.C. §112, first paragraph. *Vas-Cath v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991).

The written description rejection was discussed in sections 5-6 (pages 2-4) of the October 3, 1997 Action (Exhibit B). Although these sections purportedly address the written description rejection, they discuss whether the specification provides "guidance and direction 'how to use'" antibodies to block adhesion (see page 4, third paragraph and page 5, sixth paragraph), and further discuss where existing "guidance and direction" on other methods of use appears in the specification (page 4, fourth paragraph and page 5, fifth paragraph). Section 6 further states that "there is insufficient information or guidance as 'how to use' VCAM-1-specific antibodies" in the claimed method (page 5, second paragraph). Section 6 additionally addressed Dr. Papayannopoulou's Exhibit F declaration despite the fact that the declaration was presented on the issue of enablement rather than written description.

While consideration of "guidance and direction" and "how to use" would be proper as part of an evaluation of enablement, these issues are not properly addressed in the written description context. The Examiner thus erred in introducing these enablement-type considerations into a rejection of claims 30-33 based on alleged lack of written description. In addition, if these considerations were the basis for disregarding the declaratory evidence presented on the issue of written description, that basis was in error.

C. The Rejection for Lack of Enablement

1. The Examiner Erred in Linking the Enablement Requirement to the Written Description Requirement

The Examiner erred in linking the enablement rejection to the written description rejection because these two requirements are separate and distinct aspects of 35 U.S.C. §112. *Vas-Cath, supra.* The test for enablement is not whether there is a written description of the use but rather "whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with the information known in the art without undue experimentation." *United States v. Telectronics*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

In the October 3, 1997 Action (Exhibit B), the Examiner accepted that "the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as . . . to impede lymphocyte or tumor cell transmigration . . ." based only on statements of these uses in the specification. The Examiner also accepted that "With respect to the use of hemopoietic cells, the specification provides guidance and direction to immunoselecting primitive hemopoietic stem cells, progenitor cells and bone marrow stromal elements (page 18, lines 13-15)," based on a statement of the use. With regard to the presently claimed invention, however, the Examiner asserted a lack of guidance and direction merely because there was not an *in ipsis verbis* recitation of the claimed method (see page 5, sixth and seventh paragraphs of the Action).

The Examiner therefore erred by determining enablement based on his collateral position on written description. In order to properly evaluate enablement, the Examiner should have considered the information known in the art, and whether one of ordinary skill in the art could have used anti-VCAM-1 antibodies according to the claimed method without undue experimentation. Nowhere in the Office Actions does there appear to be a consideration of these questions.

2. The Claimed Methods Require No Undue Experimentation

According to *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered in determining whether the claimed methods require undue experimentation include (1) the quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the art, and (8) the breadth of the claims.

In this case, the nature of the invention is the blockade of interaction between two molecules by administering an antibody that binds to one of the molecules. As noted above, this is a well known therapeutic application of antibodies in general. Thus, the state of the prior art was relatively sophisticated, and the relative skill of those in the art and the methodological predictability of the art was high. The breadth of the claims is such that the only required therapeutic endpoint is a decrease in VCAM-1-mediated adhesion, in contrast to, *e.g.*, a requirement that a disease be "treated" or "cured." The general guidance and direction in the specification that VCAM-1 and VLA-4 are involved in adhesive interactions, including the specific reference to interactions between bone marrow stromal cells and hemopoietic cells, is coupled with two working examples. One example shows that an exemplary anti-VCAM-1 antibody, 6G10, binds to endothelial cells (which express VCAM-1) and blocks adhesion of lymphocytes (which express VLA-4) to activated endothelial cells by up to 80%. See Example 4 at page 15, lines 24-25 of the specification and paragraph 5 of Dr. Torok-Storb's Exhibit D declaration. The other example shows that the 6G10 antibody binds to bone marrow stromal cells (which express VCAM-1). See Example 5 at page 17, lines 3-14. Despite the absence of actual exemplary procedures specifically showing blocking adhesion of these stromal cells to hemopoietic cells (which express VLA-4), the quantity of experimentation required to actually block adhesion would have been negligible. This is confirmed by Dr. Torok-Storb's Exhibit D declaration, which states in paragraph 7 that "One of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4-VCAM-1 interaction, *e.g.*, [lymphocyte-endothelial cell interaction], to another VLA-4-VCAM-1 interaction . . ."

The specification's disclosure was thus more than sufficient for one of ordinary skill in the art to practice the claimed invention as of August 1, 1990. With respect to claim 30, a working example of blocking VCAM-1 mediated adhesion of cells expressing VLA-4 (lymphocytes) was provided in the specification. With respect to claims 32-33, no undue experimentation would have been involved in actually blocking adhesion of hemopoietic cells to stromal cells.

The Examiner failed to point to any specific difficulties that one of ordinary skill in the art would face in carrying out the claimed methods; it is a simple matter for one to administer an anti-VCAM-1 antibody, *e.g.*, by intravenous injection(s), and to measure the resulting release of hemopoietic cells into the peripheral blood, *e.g.*, by taking blood samples and determining the number of hemopoietic colony forming units in each sample. One of ordinary skill in the art would have easily been able to titrate the dosage of antibody to any desired level of release.

The fact that those of ordinary skill in the art could have carried out the claimed methods easily and without undue experimentation is confirmed by Dr. Papayannopoulou's Exhibit F declaration. Paragraph 4 of the declaration states that, in light of the knowledge conveyed by the application, one of ordinary skill in the art as of August 2, 1990 would readily have been able to administer an amount of anti-VCAM-1 antibody effective to achieve the therapeutic endpoint, which is the decrease of VCAM-1-mediated adhesion between stroma and hemopoietic precursors, resulting in mobilization of hemopoietic cells.

Paragraphs 5 and 6 of Dr. Papayannopoulou's Exhibit F declaration reference data reported in her previous declaration signed November 30, 1995 (attached to the Appellants' response filed December 22, 1995) as well as data reported in Papayannopoulou *et al., Proc. Nat'l. Acad. Sci (USA), 92*:9647-9651 (1995) (Exhibit 1 to her declaration). She states that these data, obtained with two different antibodies, 6G10 and MK/2, confirm that one of ordinary skill in the art could readily have practiced the claimed methods *in vivo*. Systemic administration of either antibody to mice caused release of bone marrow progenitor cells from the bone marrow to the peripheral blood, as measured by counting hemopoietic colony forming units in peripheral

blood samples. Dr. Papayannopoulou further states in both paragraphs 5 and 6 that "no undue experimentation was involved in order to achieve this therapeutic endpoint."

The only specific issue raised by the Examiner was that "The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods." As discussed above, the therapeutic endpoint recited in the claims is a decrease in VCAM-1-mediated adhesion. One of ordinary skill in the art would easily have been able to determine the level of decrease in adhesion needed to achieve any desired clinical effect. This is confirmed by Dr. Papayannopoulou's Exhibit F declaration, which states in paragraph 4 that "It would have required no more than routine experimentation for the ordinary skilled worker to determine what therapeutic conditions would provide a desired level of measured response." In addition, Dr. Torok-Storb's Exhibit E declaration demonstrates that one of ordinary skill in the art would have known both the clinical conditions to which this method is applicable and the desired therapeutic endpoints.

Paragraph 4 of Dr. Torok-Storb's Exhibit E declaration briefly describes the process of bone marrow transplantation. Bone marrow is harvested from the donor by direct aspiration from the bone. This bone marrow may be subjected to various procedures to render it enriched in primitive stem cells and hematopoietic progenitor cells. The recipient's immune system, including the hemopoietic cells in the bone marrow, is destroyed to prepare the recipient for transplantation. This destruction is accomplished either through total body irradiation, chemotherapy (*e.g.*, cyclophosphamide treatment), or administration of anti-thymocyte globulin (which binds to and facilitates the destruction of the recipient's lymphocytes via the recipient's own complement system). The donor's bone marrow cells are then infused intravenously into the recipient's bloodstream.

In paragraph 6, Dr. Torok-Storb states that one of ordinary skill in the art, after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells, would have understood from the disclosure in the application that a clear therapeutic benefit of administering anti-VCAM-1 antibody to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of hemopoietic progenitor/stromal cell binding. The consequential release of bone marrow cells into the bloodstream would allow those cells to be

harvested directly from the blood of a donor. The advantages attendant upon this harvesting method are numerous: it is easier to harvest cells from blood than from bone marrow, the cells harvested are already conditioned to be in the blood (a desirable attribute because donor bone marrow is infused into the recipient's bloodstream), and the cells released are already enriched in primitive stem cells and progenitor cells.

Dr. Torok-Storb also notes in paragraph 6 that one of ordinary skill in the art would likely view an antibody-mediated decrease in bone marrow cell adhesion to be a therapeutic method even more easily employed in donors than in recipients, because the mere release of bone marrow cells is an adequate therapeutic endpoint with regard to harvest from the donor. However, in combination with additional destructive step (destroying the immune-related bone marrow cells and other cells of the immune system using means known in the art), the antibody-mediated release of bone marrow cells would also have been understood to have therapeutic benefit in recipients.

Thus, Appellants' declaratory evidence of record demonstrates that no undue experimentation would have been required for one of ordinary skill in the art to practice the claimed methods, and that those of ordinary skill in the art would also have known what clinical conditions the claimed methods would be applicable to and what therapeutic endpoint would be necessary to achieve the desired effects.

3. The Examiner Erred by Summarily Dismissing the Declaratory Evidence Addressing Enablement

The Examiner erred by summarily dismissing the substantial declaratory evidence supporting enablement of the claimed invention. The Examiner did not identify any errors or deficiencies in the declarations, nor did he point to any specific difficulties that one of ordinary skill in the art would encounter when carrying out the claimed methods. The Examiner also failed to supply any rebuttal evidence. Upon consideration of the totality of the record, including the uncontroverted declaratory evidence, it is clear that the rejection under 35 U.S.C. §112, first paragraph, for lack of enablement should be reversed with respect to each of claims 30-33.

Conclusion

The above remarks are believed to establish that each of claims 30-33 satisfy the written description and enablement requirements of Section 112, and that the Examiner's rejections on both of these grounds should be reversed.

Respectfully submitted,

MARSHALL, O'TOOLE, GERSTEIN,
MURRAY & BORUN

By 

Li-Hsien Rin-Laures, M.D.
Registration No. 33,547
Attorney for Appellants
6300 Sears Tower
233 South Wacker Drive
Chicago, Illinois 60606-6402
(312) 474-6300

Chicago, Illinois
July 8, 1998

Exhibit A

RECYCLED PAPER
RECYCABLE

EXHIBIT A

Currently pending claims of U.S. Serial No. 08/448,649

30. [FOUR TIMES AMENDED] A method of blocking interaction between a bone marrow stromal cell expressing VCAM-1 and a cell expressing VLA-4, which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and the cell expressing VLA-4.

31. The method of claim 30 wherein the antibody to VCAM-1 is selected from the group consisting of monoclonal antibodies and antigen-binding fragments of said monoclonal antibodies that specifically bind to an epitope recognized by 6G10 monoclonal antibody produced by hybridoma ATCC No. HB 10519.

32. [TWICE AMENDED] The method of claim 30 wherein the cell expressing VLA-4 is a hemopoietic cell expressing CD34 antigen.

33. [TWICE AMENDED] The method of claim 30 wherein the cell expressing VLA-4 is a hemopoietic stem cell or a hemopoietic progenitor cell.

Exhibit B.

RECYCLED PAPER
RECYCABLE

OCT 07 1997

MARSHALL O'TOOLE

08/448649

UNITED S[illegible] DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/448,649	05/24/95	MASINOVSKY	B 27866/32663

EXAMINER	
GAMBEL, P	
ART UNIT	PAPER NUMBER
1806	29

DATE MAILED: 10/03/97

18M1/1003

MARSHALL O'TOOLE GERSTEIN
MURRAY & BORUN
[illegible]00 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO IL 60606-6402

OIPE OCT 10 1997 PATENT & TRADEMARK OFFICE

MAIL DATE CANCELLED

OIPE JUN 10 1998 PATENT & TRADEMARK OFFICE

MAIL DATE CANCELLED

OIPE JUN 10 1998 PATENT & TRADEMARK OFFICE C35

MAIL DATE CANCELLED

OIPE JUL 10 1998 PATENT & TRADEMARK OFFICE C35

DOCKETED 10/3/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 9/14/97 (8/12/97 ARGUMENTS AND DEC UNDER RULE 132)

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☑ Claim(s) 30-33 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 30-33 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

RECEIVED JUL 22 1998 GROUP 1800

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

RECEIVED 98 JUN 21 PM 4:07 GROUP 180

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been
☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

OIPE DATE CANCELLED JUL 10 1998 PATENT & TRADEMARK OFFICE

DETAILED ACTION

1. Since this application is eligible for the transitional procedure of 37 CFR 1.129(a), and the fee set forth in 37 CFR 1.17(r) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.129(a). Applicant's first submission after final filed on 9/19/97 (Paper No. 28) has been entered.

2. Applicant's amendment, filed 9/19/97 (Paper No. 28), is acknowledged. Claims 30, 32-33 have been amended

OIPE JUL 10 1998 PATENT & TRADEMARK OFFICE

Claims 30-33 are pending and being acted upon presently.

3. The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.

This Action will be in response to applicant's arguments, filed 9/19/97 (Paper No. 28), The rejections of record can be found in the previous Office Actions (Paper Nos. 21,24,27).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the form PTO-948 previously sent in Paper No. 4.

5. Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "a method of blocking interaction between bone marrow stromal cells expressing VCAM-1 and a cell expressing VLA-4 (wherein the cell expressing VLA-4 is a hemopoietic precursor cell) (wherein the cell expressing VLA-4 is a hemopoietic precursor cell expressing CD34 antigen) which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and the cell expressing VLA-4".

Applicant 's amendment, filed 9/19/97 (Paper No. 28) similarly to applicant's amendment, filed 12/12/96 (Paper No. 23), has directed support for the amended claims to the following.

RECEIVED
JUL 22 1998
GROUP 1800

(1) page 4, lines 11-16; however said passage refers to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors;

Applicant also argues that the expression of VLA-4 on lymphocytes is noted throughout the specification. However, the claims are drawn to "cells", "a hemopoietic precursor cell", or "a hemopoietic precursor cell expressing CD34 antigen". The examiner agrees that the instant specification discloses inhibiting lymphocyte adherence and migration, however the claims are not drawn to lymphocytes but rather drawn to cells other than lymphocytes. For example, as previously noted; page 14, lines 28-32 similarly refers to blocking lymphocyte adhesion and not hemopoietic precursors.

(2) page 5, lines 14-15 which refers to Figure 12 as described in Example 5 and page 17, lines 24-30 which states: "VLA-4 ... is expressed at high levels on bone marrow cells bearing the CD34" and "that CD34 expression distinguishes a subset of bone marrow cells (1-4% which are enriched in primitive stem cells and progenitors"

In contrast to applicant's reliance on the instant disclosure including Example 5 and the expression of VLA-4 on hemopoietic cells; the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as to prevent modulating the immune response or to impede lymphocyte or tumor cell transmigration (see Summary of the Invention, particularly page 4, lines 17-22). With respect to the use of hemopoietic cells, the specification provides guidance and direction to immunoselecting primitive hemopoietic stem cells, progenitor cells and bone marrow stromal elements (page 18, lines 13-15).

Therefore, the examiner maintains that there does not appear to be support for interfering with hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion such as useful in inhibiting GVHD and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion.

Applicant is required to cancel the new matter in the response to this Office action.

6. Applicant 's amendment, filed 9/19/97 (Paper No. 28), also relies upon the submission or applicant's arguments and declaratory evidence, filed 8/22/97 (Paper No. 26).

Applicant's amendment in conjunction with the Torok-Storb and the Papayannoupoulo declarations under 37 C.F.R. § 1.132, filed 8/22/96 (Paper No. 26), have been fully considered but are not found convincing.

Similar to her previous declaration (Paper No. 20), Torok-Storb states that one of ordinary skill in the art would understand from reading the application that anti-VCAM antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved and that one of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4-VCAM-1 interaction to another (Paper No. 26).

Papayannoupoulo states that in light of the knowledged conveyed by the application, one of ordinary skill in the art as of the priority date would readily have been able to administer an amount of anti-VCAM-1 antibody effective to achieve the therapeutic endpoint, which is the decrease of VCAM-1-mediated adhesion between stroma and hemopoietic precursors, resulting in mobilization of hemopoietic cells. This declaration also relies upon evidence that the systemic administration of anti-VCAM-1 antibodies can release bone marrow progenitor cells from the marrow to the peripheral blood.

The examiner maintains that the application as filed does not provide written description nor guidance and direction on "how to use" anti-VCAM-1 to block any VCAM-1-mediated adhesion, regardless of the type of cells involved, to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells.

As pointed out above in section 5 and of record, the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as to prevent modulating the immune response or to impede lymphocyte or tumor cell transmigration (see Summary of the Invention, particularly page 4, lines 17-22). With respect to the use of hemopoietic cells, the specification provides guidance and direction to immunoselecting primitive hemopoietic stem cells, progenitor cells and bone marrow stromal elements (page 18, lines 13-15).

Again, an amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. This is not the same from introducing subject matter never present in the specification as filed where no apparent error existed. Obviousness is not the standard for addition new limitations to the disclosure as filed. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Adding information to the specification not supported by the disclosure as filed is considered new matter in that introduces new concepts violate the description requirement of the first paragraph of 35 U.S.C. 112.

In addition, the application must be enabled at the time the invention was made.

6. The specification is objected to and claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention essentially for the reasons of record set forth in the previous Office Actions (Paper Nos. 21, 24, 27).

As indicated above in sections 5 and 6, there is insufficient information or guidance as "how to use" VCAM-1-specific antibodies in "a method of blocking interaction between a bone marrow stromal cells expressing VCAM-1 and a cell (hemopoietic precursor cell, hemopoietic stem or progenitor cells) expressing VLA-4 which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and a cell expressing VLA-4".

Applicant 's amendment, filed 9/19/97 (Paper No. 28), in conjunction with the submission of applicant's arguments and declaratory evidence, filed 8/22/97 (Paper No. 26) have been fully considered but are not found convincing for the reasons of record and reiterated above.

The application must be enabled at the time the invention was made.

As pointed out above in sections 5 and 6 and of record, the specification provides guidance and direction to applying the use of VCAM-1-specific antibodies to prevent GVHD (page 18, lines 11-12) as well as to prevent modulating the immune response or to impede lymphocyte or tumor cell transmigration (see Summary of the Invention, particularly page 4, lines 17-22). With respect to the use of hemopoietic cells, the specification provides guidance and direction to immunoselecting primitive hemopoietic stem cells, progenitor cells and bone marrow stromal elements (page 18, lines 13-15).

The examiner maintains that the application as filed does not provide written description nor guidance and direction on "how to use" anti-VCAM-1 to block any VCAM-1-mediated adhesion, regardless of the type of cells involved, to release bone marrow progenitor cells from the marrow to the peripheral blood or to mobilize hemopoietic cells.

Therefore, the specification as filed does not provide any guidance on "how to use" the VCAM-1 specific antibodies in the manner encompassed by the claims or argued by applicant in conjunction with Torok-Storb and Papayannoupoulo or any other manner as encompassed by the claimed methods. The specification is drawn to inhibiting lymphocyte adherence not hemopoietic stem and progenitor cell adherence. The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods.

Applicant's arguments are not found persuasive.

7. Upon reconsideration of the art and applicant 's amendments, filed 9/19/97 (Paper No. 28) and filed 8/22/97 (Paper No. 26); the previous rejection of claims 30 and 32-33 under 35 U.S.C. 112, first paragraph, for the scope of VCAM-1-specific antibodies has been withdrawn.

8. No claim allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 305-3014 or (703) 308-4242.

Communications via Internet e-mail regarding this application, other than those under 35 U.S.C. 132 or which otherwise require a signature, may be used by the applicant and should be addressed to [**lila.feisee@uspto.gov**].

All Internet e-mail communications will be made of record in the application file. PTO employees do not engage in Internet communications where there exists a possibility that sensitive information could be identified or exchanged unless the record includes a properly signed express waiver of the confidentiality requirements of 35 U.S.C. 122. This is more clearly set forth in the Interim Internet Usage Policy published in the Official Gazette of the Patent and Trademark on February 25, 1997 at 1195 OG 89.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
September 30, 1997

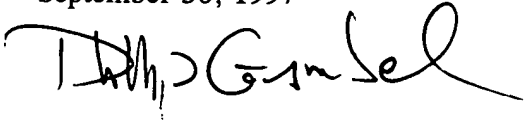


Exhibit C.

RECYCLED PAPER
RECYCABLE

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

08/448,649

APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
08/448,649	05/24/95	MASINOVSKY	B 27856/32663

EXAMINER

18M1/0320

MARSHALL O'TOOLE GERSTEIN
MURRAY & BORUN
6300 SEARS TOWER
233 SOUTH WACKER DRIVE
CHICAGO IL 60606-6402

GAMBEL, P.

ART UNIT	PAPER NUMBER
1806	24

DATE MAILED: 03/20/97

MAIL DATE CANCELED JUN 10 1998 PATENT AND TRADEMARK OFFICE JC35

RECEIVED MAR 25 1997 MARSHALL O'TOOLE

OIPE JUL 10 1998 PATENT AND TRADEMARK OFFICE JC35

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

Docketed: 6-20-97

OFFICE ACTION SUMMARY

☑ Responsive to communication(s) filed on 12/12/96

☑ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

RECEIVED JUL 22 1998 GROUP 1800

Disposition of Claims

☑ Claim(s) 30-33 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☑ Claim(s) 30-33 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

RECEIVED 98 JUL 21 AM 8:01 GROUP 180

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☐ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

–SEE OFFICE ACTION ON THE FOLLOWING PAGES–

OIPE
DATE CANCELLED
JUN 1998
PATENT & TRADEMARK OFFICE

DETAILED ACTION

The Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1806.

2. Applicant's amendment, filed 12/12/96 (Paper No. 23), is acknowledged.
Claims 30, 32-33 have been amended

OIPE
JUL 10 1998
JC35
PATENT & TRADEMARK OFFICE

Claims 30-33 are pending and being acted upon presently.

The text of those sections of Title 35 USC not included in this Action can be found in a prior Office Action.
This Action will be in response to applicant's arguments, filed 12/12/96 (Paper No. 23), The rejections of record can be found in the previous Office Action (Paper No. 21).

4. Formal drawings and photographs have been submitted which fail to comply with 37 CFR 1.84. Please see the enclosed form PTO-948.

5. Claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, as the specification does not contain a written description of the claimed invention, in that the disclosure does not reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention at the time the application was filed. The specification as originally filed does not provide support for the invention as now claimed: "a method of interfering with interaction between a bone marrow stromal cells expressing VCAM-1 and a hemopoietic precursor cell which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and hemopoietic precursor cell".

Applicant 's amendment, filed 12/12/96 (Paper No. 23), has directed support for the amended claims to (1) page 4, lines 11-16; however said passage refers to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors; (2) page 14, lines 28-32 which similarly refers to blocking lymphocyte adhesion and not hemopoietic precursors; and (3) page 17, lines 24-33 which refers to the expression of VLA-4 on human CD34+ bone marrow cells and infer that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements and go on further to disclose the use of VCAM-1-specific antibodies to prevent GVHD.

RECEIVED
JUL 22 1998
GROUP 180

There does not appear to be support for interfering with hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion such as useful in inhibiting GVHD and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion.

Applicant's amendment in conjunction with the Torok-Storb declaration under 37 C.F.R. § 1.132, filed 12/12/96 (Paper No. 23), have been fully considered but are not found convincing. Torok-Storb states that one of ordinary skill in the art after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells and their involvement in mediating adhesive interactions between hemopoietic cells and stromal elements would have understood from the disclosure in the application that a clear therapeutic benefit of administering VCAM-1-specific antibodies to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding.

An amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of error in the specification, but also the appropriate correction. This is not the same from introducing subject matter never present in the specification as filed where no apparent error existed. Obviousness is not the standard for addition new limitations to the disclosure as filed. The instant claims now recite limitations which were not clearly disclosed in the specification as-filed, and now change the scope of the instant disclosure as-filed. Adding information to the specification not supported by the disclosure as filed is considered new matter in that introduces new concepts violate the description requirement of the first paragraph of 35 U.S.C. 112.

Applicant is required to cancel the new matter in the response to this Office action.

6. The specification is objected to and claims 30-33 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention. In evaluating the facts of the instant case, the following is noted:

As indicated above in section 5 in the new matter rejection, there is insufficient information or guidance as how to use VCAM-1-specific antibodies in "a method of interfering with interaction between a bone marrow stromal cells expressing VCAM-1 and a hemopoietic precursor cell which comprises administering an antibody to VCAM-1 in an amount effective to decrease VCAM-1-mediated adhesion between the bone marrow stromal cell and hemopoietic precursor cell".

As indicated above in section 5, Torok-Storb states that one of ordinary skill in the art after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells and their involvement in mediating adhesive interactions between hemopoietic cells and stromal elements would have understood from the disclosure in the application that a clear therapeutic benefit of administering VCAM-1-specific antibodies to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding.

However the specification as filed does not provide any guidance on how to use the VCAM-1 specific antibodies in this manner as described by Torok-Storb or any other manner as encompassed by the claimed methods. The specification is drawn to inhibiting lymphocyte adherence not hemopoietic stem and progenitor cell adherence. The disclosure does not provide direction or guidance as to which therapeutic conditions and what therapeutic endpoints are would be appropriate for the claimed methods.

Therefore, in addition to the new matter rejection set forth above,
The specification does not teach how to extrapolate data obtained from in vitro binding studies of marrow stromal elements to the development of effective in vivo therapeutic methods to interfere with hemopoietic cell-marrow stroma interactions, commensurate in scope with the claimed invention. Undue experimentation would be required to practice the claimed methods with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively practice the claimed methods and absent working examples providing evidence which is reasonably predictive that the claimed methods are effective for interfering with inhibiting with hemopoietic cell-marrow stroma interactions in a therapeutic method.

7. Claims 30 and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for VCAM-1-specific antibody 6G10 or antigen-binding specificities like 6G10 (Example 5) to bind marrow stromal elements does not reasonably provide enablement for any other VCAM-1-specific antibodies for the reasons of record set forth in the last Office Action (Paper No. 6) as they apply to the newly amended claims.

Applicant's arguments, filed 12/12/96 (Paper No. 23),have been fully considered but are not found convincing.

Applicant argues in conjunction with In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988) that it would not be undue experimentation to enable other VCAM-1-specific antibodies that bind to human marrow stromal cells. Applicant also likens the instant application to Example J of USPTO Traning Materials for Enablement (Fall, 1990). However for the reasons of record and those set below, the rejection is based upon limiting the scope to the particular VCAM-1 specificity and not to a particular VCAM-1-specific antibody. The rejection is based upon sound scientific reasoning and the evidence of record in the instant application. The

specification discloses that other VCAM-1-specific antibodies which recognize VCAM-1 on human endothelium do not bind significantly to human bone marrow stroma (Example 5). Therefore, the antigenic epitope recognized by the 6G10 antibody appears unique compared to other VCAM-1-specific antibodies. Applicant's claimed specificity is not consistent and commensurate in scope with applicant's own admission in the specification as-filed. Applicant is enabled only for the 6G10 antibody specificity to isolate or immunoselect of identify bone marrow stromal cells that express VCAM-1.

Applicant argues that Liesveld et al. (Blood, 1993) does show the VCAM-1-specific antibody 4B9 does bind to marrow stroma and was able to partially inhibit binding of a myeoblastic cell lines to marrow stroma some inhibition. However, Liesveld et al. discloses that VCAM-1-specific antibodies was not able to inhibit the adhesion of other cell types and in particular CD34+ cells (see entire document, page 116, column 2, Normal CD34+ progenitors). The claimed hemopoietic precursors are encompassed by these normal CD34+ progenitors.

Applicant argues that Simmons et al. (Blood, 1992) does teach the inhibition of hemopoietic cells adherence to marrow stromal elements. It is noted that such inhibition was performed under in vitro conditions wherein the VCAM-1 was induced to high levels with cytokines in contrast to the low levels of constitutive expression of VCAM-1 (see Abstract). Also, Simmons et al.states that is was significant that one was unable to completely block the binding of hemopoietic progenitors with VCAM-1-specific antibodies alone or in combination (Discussion).

In addition, Simmons et al., discloses that notably the molecular weight of the glycoproteins immunoprecipitated by 6G10 was 130 kD, some 20 kD larger than that of VCAM-1 expressed by endothelial cells of human and primate origin. This finding may reflect selective expression by bone marrow stroma of the recently identified VCAM-1 in a form that incorporates an additional seventh domain in its extracellular portion (page 393 (column 2, paragraph 2). Therefore, there is further evidence that the specificities associated with the 6G10 antibody for bone marrow stromal elements would not be expected with other VCAM-1-specific antibodies.

Applicant's arguments are not found persuasive as they apply to newly amended claims.

8. Similarly to what was pointed out in the last Office Action upon consideration of the art, applicant's instant claims drawn to methods of interfering with hemopoietic cell-marrow stroma interactions are free of the prior art. As disclosed in the instant specification (Example 5), known VCAM-1-specific antibodies at the time the invention was made did not bind to bone marrow stromal elements. Further, the prior art was directed towards the use of VCAM-1-specific antibodies in inhibiting inflammatory conditions and not towards inhibiting the interaction between bone marrow stromal cells and bone marrow hemopoietic cells.

9. No claim allowed.

10. Applicant's amendment necessitated the new grounds of rejection. Accordingly, **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

11. This application is subject to the provisions of Public Law 103-465, effective June 8, 1995. Accordingly, since this application has been pending for at least two years as of June 8, 1995, taking into account any reference to an earlier filed application under 35 U.S.C. 120, 121 or 365(c), applicant, under 37 CFR 1.129(a), is entitled to have a first submission entered and considered on the merits if, prior to abandonment, the submission and the fee set forth in 37 CFR 1.17(r) are filed prior to the filing of an appeal brief under 37 CFR 1.192. Upon the timely filing of a first submission and the appropriate fee of $375 for a small entity under 37 CFR 1.17(r), the finality of the previous Office action will be withdrawn. In view of 35 U.S.C. 132, no amendment considered as a result of payment of the fee set forth in 37 CFR 1.17(r) may introduce new matter into the disclosure of the application.

If applicant has filed multiple proposed amendments which, when entered, would conflict with one another, specific instructions for entry or non-entry of each such amendment should be provided upon payment of any fee under 37 CFR 1.17(r).

12. Papers related to this application may be submitted to Group 1800 by facsimile transmission. Papers should be faxed to Group 1800 via the PTO Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CMI Fax Center telephone number is (703) 308-4242 or (703) 305-7939.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phillip Gambel whose telephone number is (703) 308-3997. The examiner can normally be reached Monday through Thursday from 7:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee can be reached on (703) 308-2731. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1800 receptionist whose telephone number is (703) 308-0196.

Phillip Gambel, Ph.D.
Patent Examiner
Group 1800
March 12, 1997

LILA FEISEE
SUPERVISORY PATENT EXAMINER
GROUP 1800

Exhibit D

RECYCLED PAPER
RECYCABLE

PATENT APPLICATION
DOCKET NO. 27866/32663

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	)	For: Methods for Using Agents that Bind to VCAM-1 (Amended Title)
Boris Masinovsky et al.	)	Group Art Unit: 1815
Serial No: 08/448,649	)	Examiner: P. Gambel, Ph.D.
Filed: May 24, 1995	)	

SECOND DECLARATION OF BEVERLY J. TOROK-STORB, Ph.D., UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Beverly J. Torok-Storb, Ph.D., hereby declare as follows that:

1. I received a B.S. in biology and secondary education in 1970 and a master's degree in Secondary Education in 1971 from Edinboro State College, Edinboro, Pennsylvania. I received a Ph.D. in radiation biology and human genetics in 1975 from the University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania. From 1975 to 1976 I was a Senior Fellow at the University of Washington Department of Pathology, Seattle, Washington. At the University of Washington School of Medicine, I was a Senior Fellow at the Department of Hematology from 1976 to 1979, a Research Assistant Professor of Medicine from 1979 to 1985, a Research Associate Professor of Medicine from 1985 to 1991, and a Research Professor since 1991. At the Fred Hutchinson Cancer Research Center, Seattle, Washington, I was an Associate in Medical Oncology from 1978 to 1980, an Assistant Member from 1980 to 1984, an Associate Member from 1984 to 1991, and a Member since 1991.

I am an author or co-author of over 85 scientific publications. My honors and activities include: a National Research Service Fellowship Award from NIAMDD in 1977; a Special Fellowship from the Leukemia Society of America in 1979; a Young Investigator Award from NHLBI in 1979; Chairman of Clinical Sciences Study Section 4 (CLN4), National Institutes of Health (NIH), from 1985 to 1988; Member of the NIH Reviewer's Reserve from 1988 to 1992; Visiting Professor at the Canadian Royal Academy of Physicians and Surgeons in 1989; Visiting Professor at the University of Ulm, Ulm, Germany in 1990; Chairman of the Scientific Committee ISEH meeting in Seattle in 1990; Member of the Science Advisory Council, Pacific Science Center in 1990.

2. I have reviewed the above-identified patent application U.S. Serial No. 08/448,649, including the currently pending claims, and pages 2-3 of the Office Action dated March 20, 1997. As a result of my scientific training and experience, I am knowledgeable about bone marrow transplantation and about the interactions between bone marrow cells and bone marrow stromal cells. I am therefore qualified to discuss what one of ordinary skill in the art of bone marrow transplantation would understand from the statements made in the application as of its effective filing date, which I have been advised is August 2, 1990.

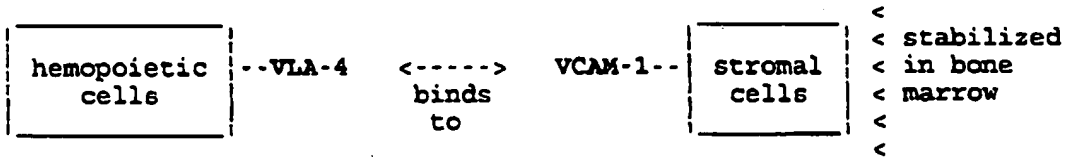
3. I make the following statements to respond to the Examiner's rejection of the currently pending claims on the basis that they are not described in the application as originally filed. Specifically, I respond to the Examiner's statements at pages 2-3 of the Office Action that:

Applicant's amendment, filed 12/12/96 (Paper No. 23), has directed support for the amended claims to (1) page 4, lines 11-16; however said passage refers to blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors; (2) page 14, lines 28-32 which similarly refers to blocking lymphocyte adhesion and not hemopoietic precursors; and (3) page 17, lines 24-33 which refers to the expression of VLA-4 on human CD34+ bone marrow cells and infer that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements and go on further to disclose the use of VCAM-1-specific antibodies to prevent GVHD.

There does not appear to be support for interfering with hemopoietic cell-stromal cell interactions with VCAM-1-specific antibodies nor is there support how the skilled artisan would use such procedures. The inhibition of adhesion mediated by VCAM-1-specific antibodies as disclosed in the specification as filed is directed towards inhibiting lymphocyte adhesion such as useful in inhibiting GVHD and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion. [Emphasis in original.]

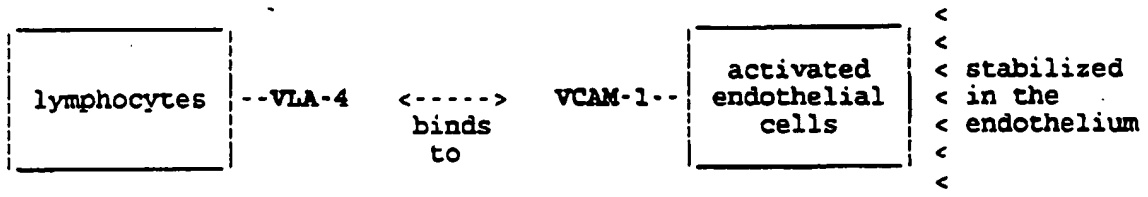
4. I agree with the Examiner's statement that the application, particularly at page 17, lines 24-33, "refers to the expression of VLA-4 on human CD34+ bone marrow cells and infer[s] that VCAM-1-VLA-4 interactions occur between hemopoietic cells and stromal elements." This interaction between hemopoietic cells (which express VLA-4) and bone marrow stromal cells (which express VCAM-1) is illustrated below (Fig. 1).

FIG. 1



5. In addition to disclosing Applicants' discovery of the role of VCAM-1 in the adhesive interaction between hemopoietic precursor cells and bone marrow stromal cells, the application also discloses that VCAM-1 mediates other adhesive interactions, such as those between lymphocytes (which express VLA-4) and activated endothelial cells (which express VCAM-1). This interaction is illustrated below (Fig. 2).

FIG. 2



The application (*e.g.*, at pages 4 and 15) also shows that anti-VCAM-1 antibodies such as 6G10 are able to block VCAM-1-mediated adhesion between lymphocytes and activated endothelial cells by up to 80%.

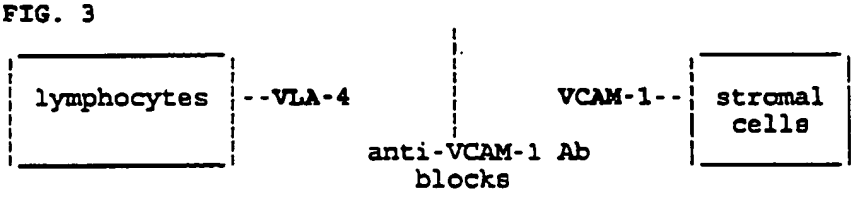
6. I strongly disagree with the Examiner's statement that the disclosed use of VCAM-1-specific antibodies to inhibit VCAM-1-mediated adhesion "is directed towards inhibiting lymphocyte adhesion . . . and not towards inhibiting hemopoietic stem and/or progenitor cell adhesion." There is no indication in the application that the use of VCAM-1-specific antibodies to interfere with, or block, intercellular adhesive interactions is limited to only some of the disclosed VCAM-1-mediated interactions and not others. On the contrary, one of ordinary skill in the art would understand from reading the application that anti-VCAM-1 antibodies are useful for blocking any VCAM-1-mediated adhesion, regardless of the type of cells involved.

7. For example, the application states at page 4, lines 11-16 that:

> The binding partners are preferably also characterized by the ability to block lymphocyte binding to cytokine-activated endothelial cells, and most preferably by binding to human VCAM-1 and to IL4- or TNFα-activated bone marrow stromal cells. A representative embodiment of this most preferred binding partner is mAb 6G10 . . .

The Examiner has characterized this passage as referring to "blocking lymphocyte binding to activated bone marrow stromal cells and not hemopoietic precursors." This statement is illustrated below.

FIG. 3



I disagree with the Examiner. One of ordinary skill in the art as of August 2, 1990 would have clearly understood upon reading the application, particularly the quoted portion at page 4, lines 11-16, that the Applicants taught use of anti-VCAM-1 antibody to inhibit any VCAM-1-mediated adhesive interaction, including the disclosed adhesive interaction between stromal cells and hemopoietic precursor cells (Fig. 1) and the disclosed adhesive interaction between lymphocytes and activated endothelial cells (Fig. 2). One of ordinary skill in the art would have extrapolated results associated with blocking one VLA-4-VCAM-1 interaction, *e.g.*, that shown in Fig. 2, to another VLA-4-VCAM-1 interaction, *e.g.*, that shown in Fig. 1 or Fig. 3.

8. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Date: 8/19/97

Beverly J. Torok-Storb, Ph.D.

Exhibit F

RECYCLED PAPER
RECYCABLE

PATENT APPLICATION
DOCKET NO. 32663

IN THE UNITED STATES
PATENT AND TRADEMARK OFFICE

In re Application of:

Boris Masinovsky et al.

Serial No: 08/448,649

Filed: May 24, 1995

For: Methods for Using Agents that Bind to VCAM-1 (Amended Title)

Group Art Unit: 1815

Examiner: P. Gambel, Ph.D.

I hereby certify that this paper is being deposited with the United States Postal Service as first class mail, postage prepaid, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on

DATE:_____

_____
Li-Hsien Rin-Laures, M.D.
Registration No. 33,547
Attorney for Applicants

DECLARATION OF BEVERLY J. TOROK-STORB, Ph.D., UNDER 37 C.F.R. §1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

RECEIVED
JUL 22 1998
GROUP 1800

Sir:

I, Beverly J. Torok-Storb, Ph.D., hereby declare as follows that:

1. I received a B.S. in biology and secondary education in 1970 and a master's degree in aquatic biology in 1971 from Edinboro State College, Edinboro, Pennsylvania. I received a Ph.D. in radiation biology and human genetics in 1975 from the University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania. From 1975 to 1976 I was a Senior Fellow at the University of Washington Department of Pathology, Seattle, Washington. At the University of Washington School of Medicine, I was a Senior Fellow at the Department of Hematology from 1976 to 1979, a Research Assistant Professor of Medicine from 1979 to 1985, a Research Associate Professor of Medicine from 1985 to 1991. and a Research Professor since 1991. At the Fred Hutchinson Cancer Research

I am an author or co-author of over 85 scientific publications. My honors and activities include: a National Research Service Fellowship Award from NIAMDD in 1977; a Special Fellowship from the Leukemia Society of America in 1979; a Young Investigator Award from NHLBI in 1979; Chairman of Clinical Sciences Study Section 4 (CLN4), National Institutes of Health (NIH), from 1985 to 1988; Member of the NIH Reviewer's Reserve from 1988 to 1992; Visiting Professor at the Canadian Royal Academy of Physicians and Surgeons in 1989; Visiting Professor at the University of Ulm, Ulm, Germany in 1990; Chairman of the Scientific Committee ISEH meeting in Seattle in 1990; Member of the Science Advisory Council, Pacific Science Center in 1990.

2. I have reviewed the above-identified patent application U.S. Serial No. 08/448,649, including the currently pending claims, and the Office Action issued March 21, 1995 in the prior application U.S. Serial No. 08/051,455. As a result of my scientific training and experience, I am knowledgeable about bone marrow transplantation and about the interactions between bone marrow cells and bone marrow stromal cells. I am therefore qualified to discuss what one of ordinary skill in the art of bone marrow transplantation would understand from the statements made in the application.

3. I make the following statements to respond to the Examiner's concerns regarding how the claimed methods promote bone marrow transplantation, and what therapeutic benefit would be provided by inhibiting the interaction between bone marrow cells and bone marrow stromal cells. Specifically, I respond to the statements at page 4 of the Office Action to the effect that:

> In addition, it is not clear what is the therapeutic benefit of decreasing adhesion of bone marrow cells to bone marrow stromal cells. The disclosure appears to indicate the use of the instant 6G10 antibody

4. Briefly, bone marrow transplantation involves the following steps. Bone marrow is harvested from the donor by direct aspiration from the bone. This bone marrow may be subjected to various procedures to render it enriched in primitive stem cells and hematopoietic progenitor cells. The recipient's immune system is destroyed to prepare the recipient for transplantation. This destruction is accomplished either through total body irradiation, chemotherapy (*e.g.*, cyclophosphamide treatment), or administration of anti-thymocyte globulin (which binds to and facilitates the destruction of the recipient's lymphocytes via the recipient's own complement system). The donor's bone marrow cells are then infused intravenously into the recipient's bloodstream.

5. One of ordinary skill in the art of bone marrow transplantation as of August 2, 1990 (which I have been advised is the effective filing date of this application) would understand from reading the application, particularly at pages 4 and 17, that the Applicants had made a novel finding that VCAM-1 is expressed on human bone marrow stromal cells. Further, the ordinarily skilled person would understand from the application that VLA-4 (a major receptor for VCAM-1) is expressed at high levels on bone marrow cells, particularly on a subset enriched in primitive stem cells and progenitor cells, and that adhesive interactions between this subset of bone marrow cells and bone marrow stromal cells may be mediated by VCAM-1. For example, at page 17, lines 11-14 and 24-33, the application states:

> The IL4/TNFα-enhancement of 6G10-recognized antigen expression on the stromal cells is evident in panel A. This novel finding would not have been predicted a priori from available information about the tissue distribution of VCAM-1.
>
> . . . .
>
> Further, we have discovered that a major receptor for VCAM-1, VLA-4 (also known as integrin alpha4/beta1 (69)), is expressed at high levels on bone marrow cells bearing the CD34 antigen. . . . This finding of coexpression is significant because CD34 expression distinguishes a subset of bone marrow cells (1-4%) which are enriched in primitive stem cells and progenitors (70). Therefore, we infer that adhesive interactions within the bone marrow between hemopoietic stem cells and/or progenitor cells and stromal elements may be mediated by the binding of VLA-4 and the antigen recognized by 6G10.

With this knowledge and the further information reported in the application (*e.g.*, at pages 4 and 15) that anti-VCAM-1 antibodies such as 6G10 would block VCAM-1-mediated adhesive interactions, one of ordinary skill in the art would understand that anti-VCAM-1 antibody would be useful for blocking VCAM-1-mediated binding of bone marrow stromal cells and bone marrow cells.

6. One of ordinary skill in the art, after being informed of the discovery of VCAM-1 expression on bone marrow stromal cells, would have understood from the disclosure in the application that a clear therapeutic benefit of administering anti-VCAM-1 antibody to decrease adhesion of bone marrow cells to bone marrow stromal cells would be the interruption of progenitor/stroma binding and consequential release of bone marrow cells into the bloodstream. This antibody-mediated release of bone marrow cells would allow those cells to be harvested directly from the blood of a donor. The advantages attendant upon this harvesting method are numerous: it is easier to harvest cells from blood than from bone marrow, the cells harvested are already conditioned to be in the blood (a desirable attribute because donor bone marrow is infused into the recipient's bloodstream), and the cells released are already enriched in primitive stem cells and progenitor cells. One of ordinary skill in the art would likely view an antibody-mediated decrease in bone marrow cell adhesion to be a therapeutic method more easily employed in donors than in recipients, because the mere release of bone marrow cells is an adequate therapeutic endpoint with regard to harvest from the donor. In contrast, an additional destructive step (destroying the immune-related bone marrow cells and other cells of the immune system using means known in the art) would need to accompany treatment of the recipient. In combination with such destructive means, the antibody-mediated release of bone marrow cells would also have been understood to have therapeutic benefit in recipients.

7. I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the above-identified application or any patent issuing thereon.

Date: 12/7/95

Beverly J. Torok-Storb, Ph.D.

Exhibit F

RECYCLED PAPER
RECYCABLE